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EDITORIAL



Innovations in protective mechanical ventilation for acute respiratory distress syndrome management

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1. Introduction

Managing acute respiratory distress syndrome (ARDS) poses significant challenges due to its heterogeneous nature. As of 2024, the updated global definition of ARDS now includes patients receiving noninvasive ventilation or high-flow oxygen therapy, facilitating earlier diagnosis [1]. Despite advancements in identifying ARDS sub-phenotypes, integration of these novel entities into clinical practice remains uncertain. Moreover, effective therapies for ARDS are limited, with persistently high mortality rates [2].

Supportive therapies are now considered the cornerstone of ARDS management, with lung-protective mechanical ventilation (MV) playing a pivotal role. Lung-protective MV improves survival in ARDS by employing strategies such as a sufficiently low tidal volume (VT) [4–8 mL/kg of predicted body weight (PBW)] with low driving pressure (ΔP) (<15 cmH₂O), low plateau pressure (Pplat) (<30 cmH₂O), moderate-to-high levels of positive end-expiratory pressure (PEEP), and prone positioning [1,3]. Additional variables (such as energy and mechanical power derived from individual parameters) appear promising to inform tailored MV settings, although their impact on patient outcomes remains to be fully elucidated [4].

Given the limited and uncertain panorama of pharmacological therapies for ARDS, innovative ventilation systems offer potential to optimize MV strategies. It is time to move beyond the traditional ‘one size fits all’ approach in MV and consider inter-individual variability to mitigate lung stress, strain, and inhomogeneity.

Innovations in MV for ARDS encompass emerging technologies aimed at improving patient outcomes through personalized ventilation strategies based on individual patient characteristics and optimized ventilation parameters. These innovations include personalized MV settings that may be tailored to sub-phenotypes, heart-lung interactions, and closed-loop or automated control systems, among others.

In this editorial, we aim to summarize the most promising innovations in protective MV for patients with ARDS.

2. ARDS sub-phenotyping and lung morphology

Lung-protective MV aims to minimize mechanical stresses on delicate and inflamed lung tissue and prevent ventilator-induced lung injury (VILI) [5]. The physiological and clinical effects of ventilator settings are influenced by functional lung size and inhomogeneity. Advances in our understanding of ARDS pathophysiology have been followed by collaborative efforts to identify homogeneous subgroups of ARDS patients and tailor personalized MV strategies accordingly [3].

While safe thresholds for variables such as VT and Pplat are commonly assumed to be consistent across all ARDS patients, the loss of aeration and actual lung size are not accounted for by predicted body weight [5]. Therefore, even with restricted VT (6 mL/kg PBW), patients with reduced functional lung size are susceptible to hyperinflation. Conversely, a slightly higher tidal volume may be more beneficial than a strictly low tidal volume in patients with better preserved functional lung size to prevent a high respiratory rate. ΔP , calculated as VT divided by respiratory system compliance, correlates strongly with clinical outcomes due to its association with aerated lung size [6].

PEEP optimization aims to recruit collapsed alveoli, enhance aerated tissue for tidal ventilation, and prevent overdistension and hemodynamic impairment. However, PEEP targeting based on oxygenation, plateau pressure, ΔP , compliance, or transpulmonary pressure has been shown to have variable effects, possibly due to inter-individual variance in recruitability [3]. Therefore, responders may need higher PEEP levels, while non-responders may benefit from lower PEEP levels, though optimizing these targets at the bedside remains challenging [3].

Distinguishing pulmonary from extra-pulmonary ARDS on the basis of lung injury etiology initially suggested higher chest wall elastance and recruitability in extra-pulmonary ARDS, but recent data no longer support this distinction [7]. Instead, recruitability correlates more closely with the severity

Table 1. Association between sub-phenotypes and MV settings.

Sub-phenotype	Characteristics	MV Setting Recommendations	Response to PEEP	Clinical Outcome
Phenotype 1 (Non-recruitable)	Reduced respiratory system elastance, high alveolar dead space, limited recruitable lung capacity	Lower PEEP levels	Low recruitability	Lower ICU mortality
Phenotype 2 (Recruitable)	Increased respiratory system elastance, enhanced compliance and PaO ₂ /FiO ₂ ratio, better lung ventilation	Higher PEEP levels	High recruitability	Higher ICU mortality
Focal ARDS	Localized injury, lower respiratory system elastance	Lower PEEP levels, avoid aggressive recruitment maneuvers	Lower recruitability	Lower overall mortality
Diffuse ARDS	Widespread injury, higher respiratory system elastance	Higher PEEP levels, aggressive recruitment maneuvers	Higher recruitability	Higher overall mortality

PEEP, positive end-expiratory pressure; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; PaO₂, partial pressure of oxygen; FiO₂, fraction of inspired oxygen.

of ARDS rather than its etiology [8]. Sub-phenotyping ARDS by focal or diffuse lung morphology reveals that patients with diffuse ARDS often exhibit higher recruitability compared to those with a focal etiology. Consequently, these patients may benefit more from high PEEP and recruitment maneuvers. The groundbreaking LIVE study stratified ARDS patients by lung morphology to compare personalized lung-protective MV tailored to lung morphology versus conventional lung-protective MV. However, misclassification of 21% of patients may have contributed to the absence of mortality reduction despite personalized MV strategies [9], and mortality rates were highest in those patients who received the ‘wrong’ personalized care.

Computed tomography (CT) remains the gold standard for assessing recruitability. Advanced imaging modalities such as electrical impedance tomography (EIT) are under investigation to guide ventilation strategies. EIT provides real-time imaging of lung ventilation and regional lung function, facilitating optimization of ventilation settings and detection of lung overdistension or collapse [3]. A meta-analysis of randomized and non-randomized studies concluded that EIT improves respiratory mechanics by enabling personalized, real-time PEEP adjustments that correlate with reduced mortality rates [10].

A recent study applied latent class analysis to 54 variables derived from respiratory mechanics, gas exchange, and CT scans of ARDS patients and identified distinct phenotypes, with phenotype 2 (recruitable) exhibiting reduced respiratory system elastance, alveolar dead space, and potentially recruitable lung capacity. Following a standardized recruitment maneuver, patients with phenotype 2 demonstrated improved ventilated lung tissue, compliance, and oxygenation, albeit with increased ICU mortality compared to phenotype 1 (non-recruitable) [11]. Table 1 summarizes the association between ARDS sub-phenotypes and MV settings.

3. Heart-lung interactions

Heart-lung interactions refer to the complex relationship between respiratory system mechanics and cardiac function [12]. In patients with ARDS, the existence of right ventricle (RV) alterations, often caused by increased pulmonary vascular resistance (PVR) with impaired gas exchange, may influence the choice of MV settings [13]. MV is frequently required for treating patients with RV failure, although it might have negative hemodynamic consequences. MV per se, and PEEP in

particular, decrease venous return and RV preload. In addition, acidemia and elevations in transpulmonary pressures with MV both increase PVR and RV afterload [12].

From a physiological point of view, the parietal pleura surrounds the chest wall and diaphragm, whereas the visceral pleura surrounds the lungs. Pleural pressure (P_{PL}) is continually exerted on the heart chambers, as well as the intrathoracic arteries and veins. Because they have very high compliance, variations in P_{PL} over the respiratory cycle result in comparable pressure changes to these structures. Venous return is determined by the pressure gradient between the right atrium (PRA) and the systemic veins (mean systemic filling pressure, MSFP), as well as venous resistance. During a positive pressure breath, the increase in P_{PL} raises PRA, reducing the pressure gradient that drives venous return and lowering RV preload. The addition of PEEP accelerates the rise in P_{PL} and PRA [12,13]. The most significant predictor of RV afterload is pulmonary vascular resistance, which can be classified into two compartments: alveolar and extra-alveolar. During MV, alveolar pressure (P_{ALV}), P_{PL} , and transpulmonary pressure ($P_{ALV} - P_{PL}$) gradually increase. The P_{ALV} acts as a backflow pressure during MV because the application of positive pressure causes an increase in West zones 2 and 1 at the expense of zones 3 and 2 [13]. PVR rises as lung volume and transpulmonary pressure rise because the alveolar arteries’ increasing resistance exceeds the extra-alveolar vessels’ declining resistance. The decreased RV afterload and reduced left ventricular filling led to a decrease in left ventricular preload and afterload, with possible hemodynamic impairment and cardiogenic shock [13].

From a clinical perspective, to mitigate the negative effects of MV on RV, using low PEEP and low VT allows for safely limiting airway pressure. This approach significantly improves prognosis and decreases the incidence of acute *cor pulmonale* in ARDS patients. Notably, application of at least a low PEEP, even if non-recruiters, over zero PEEP (ZEEP) is always recommended as it enhances overall pulmonary blood flow [12]. Another consideration is to avoid using excessively low respiratory rates, which may lead to significant acidemia. Conversely, excessively high respiratory rates should also be avoided, as they can increase intrinsic PEEP and mechanical power. Furthermore, intermittent periods of prone positioning can help periodically empty the uppermost, most exposed portions of the pulmonary vascular bed, by revering hydrostatic pressure [12].

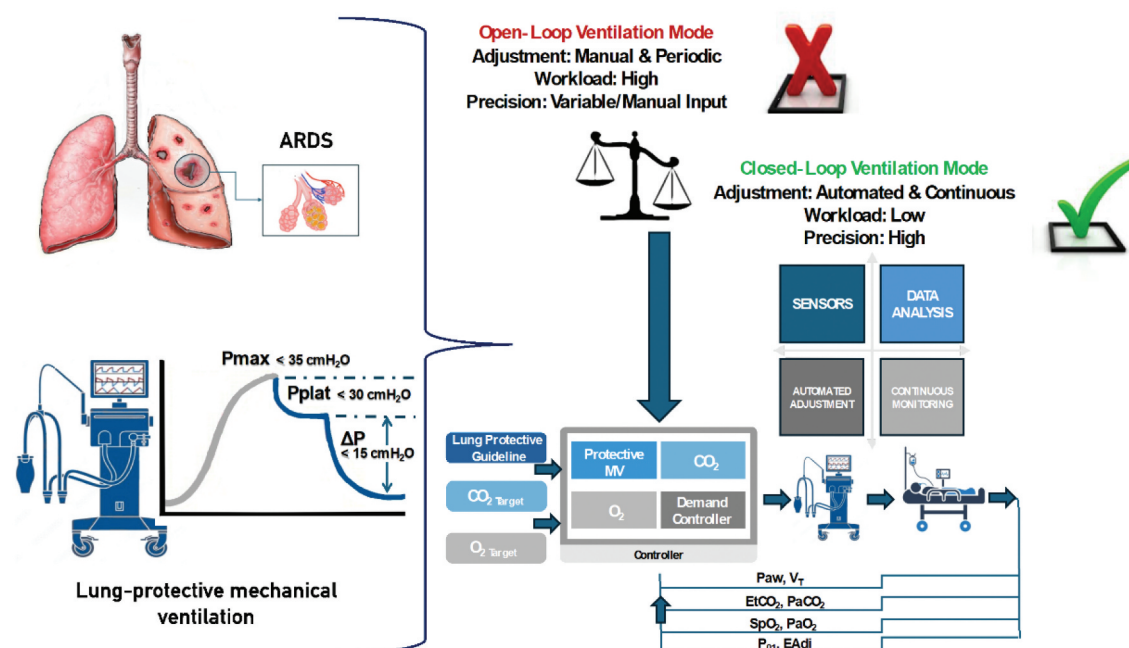


Figure 1. Potential advantages of closed-loop systems for management of MV in patients with ARDS. The figure compares open-loop and closed-loop ventilation modes, highlighting the benefits of automated and continuous adjustments in closed-loop systems for reducing workload and increasing precision. Key components include sensors, data analysis, automated adjustment, and continuous monitoring, which integrate lung-protective guidelines and target settings for carbon dioxide (CO_2) and oxygen (O_2). Measurement signals, including airway pressure (paw), tidal volume (V_T), end-tidal CO_2 (EtCO_2), arterial partial pressure of carbon dioxide (PaCO_2), peripheral saturation of oxygen (SpO_2), and arterial partial pressure of oxygen (PaO_2), are fed back to the controller and categorized according to the control targets, enabling real-time adjustments by the central controller. ARDS, acute respiratory distress syndrome; ΔP , driving pressure; MV, mechanical ventilation; EAdi, electrical activity of the diaphragm.

4. Closed-loop control systems

Closed-loop control systems utilize real-time patient data and algorithms to adjust key ventilation parameters automatically. These systems continuously monitor and adjust variables such as V_T , respiratory rate, airway pressure, respiratory mechanics, or oxygenation and dynamically adjust specific ventilatory parameters according to the patient's condition and response to ventilation. By monitoring parameters associated with VILI, closed-loop systems can mitigate further lung injury without continuous manual adjustment by clinicians [14,15].

A recent single-center randomized crossover trial compared closed-loop ventilation with conventional pressure-controlled ventilation over a 4-hour period in early ARDS. INTELLiVENT-ASV, the closed-loop ventilation mode used in this study, reduced transpulmonary ΔP , inspiratory transpulmonary pressure, and respiratory rate, thereby lowering ventilation intensity [15]. During the early stages of the COVID-19 pandemic, closed-loop MV by means of INTELLiVENT-ASV was associated more effective lung-protective outcomes compared to conventional MV (odds ratio 1.79; 95% CI 1.76–1.82; $p < 0.001$) [16].

A recent systematic review of 51 randomized trials comparing closed-loop to conventional ventilation modes confirmed that closed-loop systems have the potential to reduce the workload associated with ventilation and are as accurate as physicians at adjusting ventilator settings [14]. Closed-loop oxygen control systems enhance the percentage of time spent at optimal SpO_2 levels and may reduce healthcare workload in comparison

with manual titration [17]. However, their impact on patient outcomes remains uncertain, necessitating further investigation [14]. Figure 1 illustrates the potential advantages of closed-loop systems for MV management in ARDS patients.

5. Conclusions

Several innovative technologies hold promise for optimizing MV in ARDS patients, aiming to improve outcomes, reduce complications, and enhance overall management. Advances in novel imaging techniques (e.g. EIT) and ventilator strategies (e.g. closed-loop systems) offer opportunities for personalized ventilation strategies.

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Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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